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ARCHIVES OF PEDIATRICS

A MONTHLY DEVOTED TO THE

DISEASES OF INFANTS AND CHILDREN

JOHN FITCH LANDON, M.D., Editor

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RHEUMATIC-FEVER PROPHYLAXIS WITH BICILLIN® (DIBENZYLETHYLENEDIAMINE DIPENICILLIN G): SEATTLE STUDY

Clinical Investigation

Numerous investigations have shown that rheumatic-fever prophylaxis requires continuous control of streptococcal infection in the upper respiratory tract. Since the cost of such a long-term program may be a determining factor, studies of relatively inexpensive home therapy are of particular interest. One of these studies has been recently reported on by Tidwell,[1] speaking at the annual meeting of the American Medical Association, June, 1954.

Prophylactic medication to eradicate the beta-hemolytic streptococcus was given to 59 patients during the streptococcal season of 1952-1953. Tidwell reports that Bicillin, a highly insoluble salt of penicillin, was chosen for study because several clinical investigations had demonstrated it to be the most efficient agent for production of the extended penicillin blood levels required.

Of these 59 patients, 25 were acutely or chronically ill at the start of the program. Streptococcal pharyngitis was found in 1; congenital cardiac disease in 8; a history of rheumatic fever in 13; nephritis in 2; and asthma in 1.

THROAT CULTURES

Throat cultures were performed at the beginning of the investigation, as well as monthly or oftener throughout the course. Material for culture was obtained by swabbing the tonsils and posterior pharynx through the mouth under direct vision. The swabs were then streaked on the surface of blood agar plates. These cultures were found initially positive for beta-hemolytic streptococci in 5 patients.

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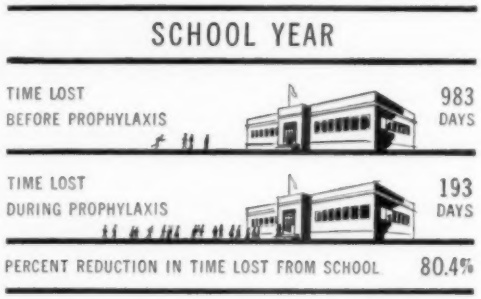
RESULTS

Tidwell relates the effectiveness of the program to the patients' school attendance. During the prophylactic course, children of school age lost only 193 days because of illness, while in the year prior to the study they had lost 983 days. School absenteeism was consequently reduced by 80.4 percent.



Of all patients, only 2 showed reappearance of the beta-hemolytic streptococcus. In the first, streptococcal breakthrough appeared after the patient had been without medication for 3 days, but the culture returned to negativity when Bicillin was resumed. In the second, the culture became negative when the dose was doubled.

No early or late suppurative or nonsuppurative sequelae followed any of the infections. There was neither recurrence of rheumatic fever nor evidence of subacute bacterial endocarditis.

Of the original 59 patients, 33 are being continued on a 5-year prophylactic program. The second streptococcal season has now been completed for these patients. Tidwell reports that the beta-hemolytic streptococcus has not reappeared in any of the cultures, and that there has been no recurrence of rheumatic fever or evidence of subacute bacterial endocarditis.

1. Tidwell, R. A.: Read before Annual Meeting of A.M.A., San Francisco, Calif., June 24, 1954.

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*Duke University study of 50 children: Dees, S.C., et al., Ann. Allergy, *11*:297, 1953.

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*Shwachman, H., Children's Hospital, Boston; The Child in Health and Disease, Grulee and Eley, 2nd Edit.

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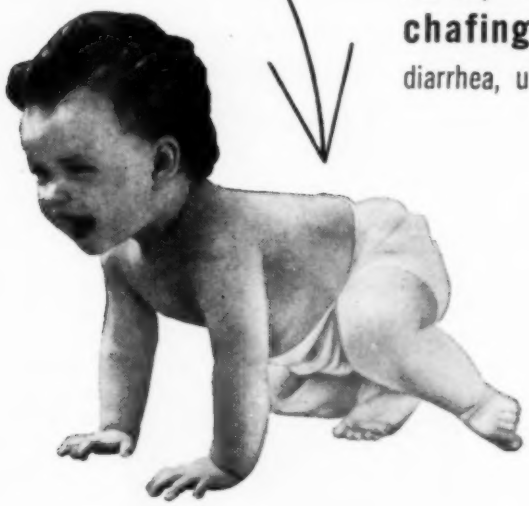

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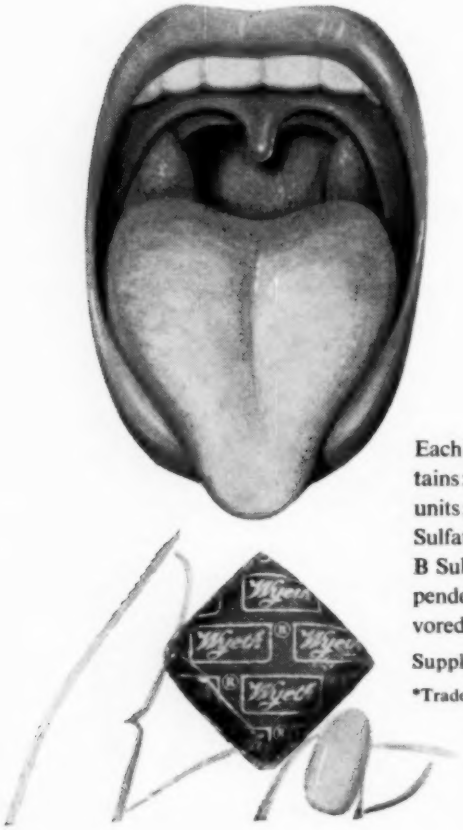

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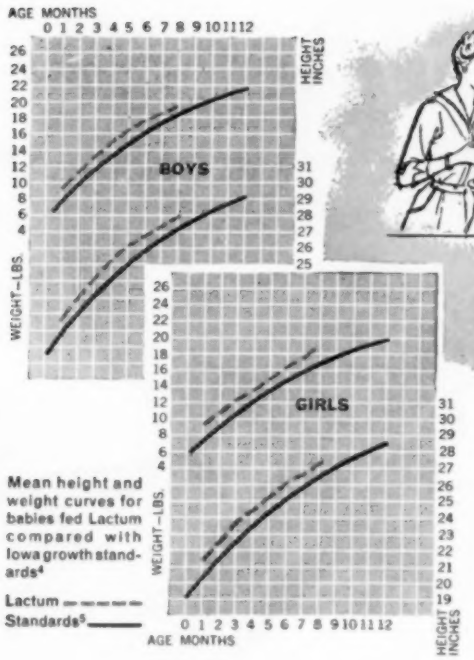

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SLIPPING OF UPPER FEMORAL EPIPHYSIS

EPIPHYSIOLYSIS, EPIPHYSIOLESTHESIS, EPIPHYSEAL SEPARATION OR FRACTURE, EPIPHYSEAL COXA VARA

CARL E. MOSSE, M.D.

New York.

Bousseau[1] is credited with description of the first authentic case of traumatic separation of the capital femoral epiphysis in 1867. But only after the x-ray was discovered was it possible to separate this affection of the hip from others like tuberculosis or coxa vara, chondrodystrophy or from coxa plana (Legg-Perthes-Calve's disease).

According to Howorth[12-14], slipping of the upper femoral epiphysis is a disease of adolescence in which there is softening of the junctions between the epiphyseal plate and the neck of the femur due to a circulatory disturbance. It usually results in downward and backward displacement of the epiphyseal plate. The softening of the epiphyseal plate is called epiphysiolysis; slipping is called epiphysiolisthesis.

The pathologic features[7] are sclerosis, thickening and avascularity of the soft tissues about the neck with absence of any primary disease of bone or cartilage.

Ghormley and Fairchild[8] regard the term "slipped epiphysis" a misnomer as the epiphysis does not slip but retains approximately the same position in the acetabulum, while the neck and the shaft of the femur rotate externally and ride upward so that the new relation of the epiphysis to the neck is downward and backward and the neck forward and upward from its normal position.

The disease usually occurs shortly before or during adolescence. Klein and co-authors[17-20] observed cases in the age group of 6 to 16 years; Boyd and co-authors[2] and Howorth, 10 to 17 years. The average age of onset is given by Wilson[28] as 13½ years for boys and 11½ years for girls, and by Green[9], at 11 and 10 8/12 years, respectively. Wilson explains this difference by the earlier spurt in growth rate and correspondingly earlier maturing of the epiphysis in girls as compared with boys.

More boys than girls are affected by slipping of the femoral epiphysis. The majority of authors observed only a slight sex difference, but Boyd and co-authors had four times as many boys as girls among their cases.

The condition has been observed in Negroes and Caucasians.

Slipping of the femoral epiphysis is more common in rapidly growing children, who are tall and large for their age or overweight. They constitute about 60 to 65 per cent of the cases observed. Boyd and co-authors and others describe them as the Froehlich type without mentioning other symptoms of the syndrome. Patients are often flabby and suffer from genu valgum.

The onset of the disease, just before or during adolescence, and the frequency with which a Froehlich type of obesity was observed suggested a causal relation with hormonal disturbances. But there is no proof, and it must be kept in mind that only 60 per cent of patients affected with slipping of the upper femoral epiphysis belong to this hypogonadal constitutional type.

Fergusson and Howorth[7] tried endocrine treatment with four cases without noticing influence on the epiphysis. Wilson[28] concludes that there is no clear evidence that the endocrine factor plays any part. If patients are treated by various kinds of sex hormones, the effect upon precocious development of secondary sexual characteristics, as well as accompanying changes, are often so troublesome that orthopedic treatment seems preferable.

A mechanical and/or traumatic etiology seems to be preferred by most authors. The weight curve[8] reaches its greatest relative height during the period of adolescence, and the inclination of the epiphyseal line is increased during this period. Both factors bring additional strain on the epiphyseal line.

The integrity of the connection of any epiphysis to the shaft depends, according to Green[9], on the binding effect of the periosteum. It is possible that, with rapid growth, the periosteum

looses its firm binding character[19] and allows a displacement. Ghormley and Fairchild, who mention this conception, report about cases observed with very nearly complete separation in which the periosteum was intact.

Trauma is often described as an etiologic factor. In Green's series, five of the patients sustained a trauma of significant degree preceding first symptoms, while 21 had no trauma in their history, although for several of the latter trauma did precipitate the acute symptoms. It is certain, writes Howorth, that trauma is not the primary cause. Trauma provokes displacement in an antecedent condition. This view is shared by most authors. It is strengthened by the fact that the condition is bilateral in 15 to 20 per cent (Johnson[15] and Klein[20] and co-authors even mention 40 per cent) of the cases and that siblings have been affected[9].

According to Howorth, the first sign of the sickness is synovitis. He regards the slipping of the femoral epiphysis as due to softening and hypervascularity of the juncture of the capital epiphyseal plate and the femoral neck.

Some authors stress the possibility of an infectious etiology. Appendicitis, tonsillitis, etc. have been observed in some cases before onset of the disease, but not frequent enough to establish etiologic relation.

To illustrate the onset of the disease the following case is presented.

CASE REPORT

A.K., 12-year-old boy, had suffered from measles, varicella, mumps and repeated tonsillitis. T and A performed at 4 years. Feb. 19, 1954, otitis media. On May 11, 1954 he sustained a subluxation of the right thumb during a ball game.

Patient is tall and heavy for his age. He has abundant subcutaneous fat. His muscles are well developed, and he is rather active in athletics. Not a Froehlich type. His genitalia are normal.

Since July 10, 1954 he complained about slight pain in the right lower extremity and limped slightly, but was able to perform his normal activities without discomfort.

Examination on July 26, 1954 reveals slight limp in the right extremity. Patient complained about slight pain, but could not localize it. He hinted sometimes to the right lower limb or knee.

Physical examination revealed nothing abnormal: extension, abduction, rotation and over-extension in the hip, as well as all movements in knee and ankle, were free and without pain.

On re-examination on July 30, 1954 patient complained about pain and tenderness laterally in the right thigh, corresponding to about the middle of the shaft of the femur. No limitation of movements.

On Aug. 12, 1954 the pain had subsided, but limp had slightly increased. When lying on his back, the right extremity was kept in outward rotation. Slight pain on the extreme of internal rotation. All other movements of hip normal. No shortening of the affected limb.

R.B.C., 4,470,000; W.B.C., 7,550 (poly., 38, lymph., 59, mono., 3 Erythrocyte sedimentation rate (E.S.R.) 6 mm.

X-ray reveals the onset of slipping of the right upper femoral epiphysis in a beginning stage (Figs. 1 and 2).

From Feb. 18 1954, when his weight was 112 pounds and his length was 60 inches, to Aug. 12, 1954, when his weight was 125 pounds and his length 62 inches, he had gained 13 pounds and had grown 2 inches.

The onset of the disease is usually gradual and vague. There is a limp, with or without pain. The pain may be localized in the hip, in the anterior or lateral part of the thigh or the knee. It is often mild and may vary in its intenseness, as does the limp which changes its degree and protectiveness[13]. The patient often walks with the involved limb in external rotation.

External rotation of the thigh, as the hip is passively flexed through its arc of motion, is the most reliable sign[12]. If passive flexion of the hip is accompanied by external rotation of the extremity, the diagnosis of slipped epiphysis is highly probable. There may be pain at the extremities of passive rotation. A position of external rotation may be taken spontaneously while lying on the back.

In the more advanced cases, shortening of the affected limb, persistent external rotation or limitation of external rotation, atrophy and deformity may be expected[8]. Tenderness about the hip varies with the stage of the condition.

The slipping may be gradual, or it may be acute. The acute slipping may be superimposed on gradual slipping, or on the preslipping stage. In some cases, sudden slip is accompanied by

Figs. 1 and 2. A. K. 12 years. Slight posterior slipping of femur. Small cyst-like defects are present in proximal portion of neck. Minimal widening of epiphyseal line.

aggravation of symptoms and signs. In extreme cases, the patient is unable to bear weight, while in others no change is observed.[13]

Laboratory examinations are not helpful in the diagnosis of the condition. Most orthopedic surgeons deny changes in blood count and E.S.R. Only Howorth mentions that he found the leukocyte count 10-12,000 with a normal differential count. We found relative lymphocytosis with normal W.B.C. count in our case. In Howorth's cases, the E.S.R. was above 10 mm. in 90 per cent and as high as 40 mm., averaging 25 mm. Chapple mentions increased E.S.R[6].

The diagnosis of slipping of the upper femoral epiphysis can be confirmed only by x-ray. The first roentgenographic signs are widening and irregularity of the epiphyseal line with decalcification of the proximal end of the neck. The head is not visibly affected, the capsule is usually swollen. This is called the preslipping stage by Howorth and others, but Klein and co-authors contend that these findings are always associated with some slipping which can be detected with suitable x-ray technics. If the slipping is a posterior one, it is earlier recognized in the lateral view, while medial slipping can be better demonstrated in a-p films.

In later phases of slipping, the neck is shorter and broader on the involved side.

The degree of slipping is best recognized by comparison with the healthy side and in whatever view the biggest slipping is demonstrated, this is taken as measure.

In the more chronic cases[9], the superior and lateral angle of the femur head no longer projects above the highest point of the femoral neck. The infero-lateral angle of the head definitely projects below the inferior border of the neck in form of a "beak". Callus forms along posterior and inferior junction of head and neck.

It is understandable that early and later stages of the disease need different *treatment*.

If the epiphysis has slipped or has moved far from its physiologic place, it has to be brought back to a situation of favorable function before it can be fixed to the shaft.

If, on the other hand, the epiphysis has slipped only slightly (less than 1 cm. according to Klein and co-authors) a fixation in its present position may prevent further slipping and tide over to the time, when, with the end of adolescence, spontaneous fusion between epi- and metaphysis must happen.

The recognition of the disease in its early stages is, therefore, of great importance as it relates to the extent of orthopedic or surgical measures as well as for the final functional result.

All authors agree that, from the first, weight bearing must cease. There is no question that some cases will heal with bed rest alone. But even with strict bed rest, which is difficult to enforce in children, slipping may progress or even spontaneous epiphysiolisthesis may happen. Most authors, therefore, recommend braces or nailing or pinning with graft or metal. Some contend that their measures accelerate fusion. To report the different opinions about methods of treatment is beyond the scope of this paper, and we refer to the bibliography.

The early diagnosis of slipping of the epiphysis is apparently often missed, especially by those not familiar with the disease. It is the aim of this paper to help the pediatrician to suspect and recognize early stages of slipping of the upper femoral epiphysis.

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TREATMENT OF ACUTE OSTEOMYELITIS: INVESTIGATIONS ON PENICILLIN CONTENT IN BONE MARROW. (Archiv fur klinische Churgie, Berlin, 274: 107 (No. 2) 1953). Juch emphasizes that systemic penicillin therapy alone can be effective in osteomyelitis only if there is as yet no abscess formation. If a considerable amount of pus has accumulated, surgical measures to remove the pus are necessary. Although various therapeutic measures produce favorable results in acute osteomyelitis, a certain number of acute cases seem to become chronic. These failures are at least partly due to inadequate doses of penicillin or to the fact that the pathogenic organisms become resistant to penicillin. For penicillin therapy to be effective, it is absolutely necessary to achieve an adequate concentration of penicillin even in the medullary cavity; if penicillin concentration is insufficient, increase in the resistance of the causative organisms is likely to result. Juch compared the penicillin content in the bone marrow and in the spongy bone substance with that in the blood during the systemic administration of the antibiotic in 18 patients undergoing bone operations. The penicillin was administered intramuscularly. The penicillin content in the bone marrow was always lower than in the serum, in one instance it was only the forty-eighth part of that in the serum, the comparative figures being 0.12 and 5.76 units, respectively. The results of these investigations suggest that in acute hematogenic osteomyelitis, the penicillin content of the blood cannot be regarded as the criterion of the bacteriostatic effect. In order to obtain bacteriostatic concentrations in the bone marrow, it is necessary either to increase the systemic doses of penicillin or to introduce the antibiotic also into the medullary cavity.—*Journal A.M.A*

CANCER: THE PRECONDITIONING FACTOR IN PATHOGENESIS

A New Etiologic Approach

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Cancer (Latin for crab) is a term which has been used from time immemorial to designate an "eating ulcer" of an incurable or malignant nature. Malignancy manifests itself when certain cells, which are apparently normal and have previously functioned normally, begin to grow and multiply in an abnormal way in some part of the body, relentlessly invade the surrounding tissues and extend to other parts of the body by metastasis. The unanswered question is why do these cells behave in this manner?

Various theories of the cause have been advanced: heredity, embryonic defects, chronic infections (parasitic, bacterial or viral), physical or chemical irritation, or injury, etc. The major research of recent years is based on the concept that some intrinsic biochemical or metabolic defect in the cell initially involved is responsible for the irregular growth. Accordingly, the major objective in therapy has been to destroy the erratic cell growth by surgical, medicinal or physical means, x-ray, radium, etc., while little attention has been given to possible metabolic or nutritional etiologic factors.

Cancer of epithelial tissues (carcinoma) may arise from a number of chronic lesions: fissures, moles, senile warts, lupus vulgaris, mastitis, syphilitic or varicose ulcers, ulceration of stomach or bowel, and burns (x-ray, chemical, thermal or electrical). The most generally recognized exciting cause is chronic irritation, physical or chemical, as in soot causing chimney sweep's cancer, tobacco tars causing lung cancer, etc.

Some earlier observers believed that the growth rate of cancerous tumors was determined by the degree of release of restraints of growth, but little was known of the nature of such restraints. According to Berrill[1], "cell proliferation is itself primarily a response to changing surface relationships". He also states that "in general the role of cell division and multiplication in relation to malignancy may have been over emphasized". Thus also Borst[2] concludes that "inflammatory over-growth results from exaggerated

response to external irritants, while cancerous growth arises from loss of normal restraints to growth". Nineteenth-century writers expressed similar views. Ribbert[3] considered cancer cells as having a latent power of unlimited proliferation which became active on their being dislocated from the normal association. Thiersch[4] believed that cancer cells grew unceasingly because the connective tissues had lost the capacity to hold their proliferative powers in check.

The author of this treatise definitely concurs with the concepts of these earlier writers, but goes a step farther, and postulates the specific cause of this retentive incapacity of connective-tissue.

To better understand the situation a brief review of the histological structure of the skin and mucous membranes may be helpful. The corium, or true skin, being derived from the embryonic mesoderm, consists essentially of connective tissue containing blood vessels, hair follicles, sebacious and sweat glands, all of which provide the supporting tissue for the surface structure of epithelial cells. The latter are in stratified arrangement, the lower layer of columnar cells, known as the germinal layer, resting upon a "condensed formation of connective tissue" known as the basement membrane. This latter is comparable in function to the footing of a masonry foundation, any breach of which might result in distortion and disintegration of the superstructure. The difference in this comparison is that the living cells of the epithelium, when they lose their footing, continue their inherent proliferative propensities without the normal directional limitations of the basement membrane. This membrane normally provides a complete and continuous connective-tissue barrier underlying the entire epithelium of the skin and mucous membranes of the alimentary, respiratory and genitourinary tracts and all their glandular ramifications, thus constituting an inviolate line of demarkation between the epithelial and mesenchymal tissues. Under these conditions it is apparent that the stability and continuity of this basement membrane is a most essential feature of the anatomical formation. Any breach or disarrangement of this structure could lead to a disturbance in the orderly growth pattern of the epithelial cells, resulting potentially in an inward extension of cell growth through the breach, which is the initial stage in malignancy. Once a break-through is effected, by reason of weakness or physical injury of this connective-tissue barrier, the mesenchymal defense

mechanism, under normal conditions, goes into action to repair the breach by proliferation of new connective tissue to fill the gap with impervious scar tissue, thus preventing erratic inward growth of the disarranged epithelium. If, however, due to faulty metabolic and nutritional status of the subject, this repair mechanism is inadequate or ineffectual, as in chronic ulceration and slow healing of abrasions or lacerations, conditions then become favorable for unobstructed malignant invasion and consequent systemic metastasis.

The most definitely established physiological function of any food substance is that of the role of vitamin C in the maintenance of stability and elasticity of connective tissues generally and the growth of new scar tissue in wound healing, and this would include the bones, cartilages, muscles, vascular tissues, subcutaneous and submucous tissues,—in fact all tissues of mesenchymal origin. Deficiency of this vitamin results in instability and fragility of all such tissues by reason of the breakdown or liquefaction of "the intercellular cement substance (collagen), with easy rupture and ineffective healing of any and all such tissues. This would apply to the "condensed connective tissues" of the above-mentioned basement membrane, and its thus acquired instability and vulnerability is, we believe, the preconditioning factor in cancerogenesis. We now know that this frailty of connective tissues is "brought about through the loss of activation of the constructive phase of the protein-building enzymes, which is normally furnished by vitamin C" (Editorial, J. A. M. A., 117: 937, 1941).

The application of this same principle to the pathogenesis of the connective-tissue tumors (sarcomata) may be made in modified form in assuming the possibility of the breakdown of the intercellular cement substance which normally binds together the endothelial cells of the vascular intima and the serosa of the pleural, pericardial and peritoneal cavities, thus resulting in their erratic and malignant proliferation and dissemination by metastases. The not infrequent combined incidence of carcinoma and sarcoma, as in the carcinosarcomata, is also suggestive of a common etiology.

DISCUSSION

This hypothesis would clarify the observation that metastases of carcinomata travel mostly by the lymphatics, whereas the mesenchymal neoplasms (sarcomata) spread mostly through the

blood vessels. It would also account for the early encapsulation of certain benign tumors (fibromata), thus preventing metastasis. Later, in the event of C-avitaminosis, these same tumors may lose their protective barrier by spontaneous dissolution or by faulty surgery or cauterization, thus releasing their cellular contents to take on an infiltrating malignant course. Likewise, chronic or indolent ulcers which may have attained closure by cicatrization may break down in later life under accentuated deficiency of vitamin C, resulting in transition to malignancy. It would also explain the relatively benign nature of the scirrhus or hard carcinomata, with predominant connective-tissue stroma, as contrasted with the medullary or soft variety with predominant cellular composition, and extreme malignancy, the vitamin-C status and proportionate connective-tissue response determining the degree of malignancy. This hypothesis would also account for the hemorrhagic and ulcerative features of most cancers, since these are also characteristic signs of vitamin-C deficiency.

That physiological instability of the connective tissues is associated with deficiency of vitamin C is forcibly shown by the classical reports of Lind (1753), Willis (1667) and Poupart (1699) on their finding in scurvy. Lind reports that in autopsies on scurvy victims he found the muscles so lax and tender that they readily fell apart. He found the intestinal musculature in the same condition. He further comments: "Why the scurvy should so frequently, and in so singular manner, affect the cartilages of the ribs, so as sometimes to separate them altogether from their connection to the breast bone, . . . I own I am at a loss to account for". He also reported a number of scurvy cases in which old fracture calluses and old scar tissue had broken down. (These might have developed cancer if scurvy had not taken them sooner.) In fact Lind also cites Martini (1609) as stating that scurvy is nearly allied to the plague, as it occasions carbuncles, buboes and cancer. Willis, the great English anatomist, of "circle-of-Willis" fame, relates in his "Tractus de Scorbuto" a symptom which he had observed several times, viz.: "A crackling of the bones upon moving the joints. Even upon turning in bed, by rubbing of the vertebrae upon each other, a considerable noise was perceived, like to the rough handling of a skeleton". Poupart, the great French surgeon, whose name is linked with "Poupart's ligament", in reporting his findings in Paris scurvy victims, states: "In some,

when moved, we heard a small grating of the bones. Upon opening their cadavers the epiphyses were found entirely separated from the bones, which by rubbing against each other had occasioned this noise. In some we perceived a small low noise when they breathed. In those (post mortem) the cartilages of the strenum were found separated from the bony part of the ribs. . . . The ligaments of the joints were found corroded and loose. . . . All the young persons under 18 had in some degree their epiphyses separated from the body of the bones."

Lind's observation of the breakdown of old fracture calluses and scar tissue is confirmed by recent research by Hunt[5], who was first to observe the breakdown of previously formed scar tissue as the result of vitamin C deficiency causing liquefaction of the intercellular cement substance. More recently, Pirani and Levenson[6] studied the effect of vitamin C deficiency on previously healed wounds. Guinea pigs bearing wounds which had been healed for six weeks were subjected to a vitamin C-free diet for 26 days, by which time severe changes were observed in the area of the scar tissue. These consisted of fibroblastic proliferation, regression of connective tissue elements and hemorrhages (very suggestive of precancerous changes—W. J. McC.). Billroth, the famous 19th-century Viennese surgeon (1829-1894), recorded a somewhat similar observation. He had expressed the belief that cancer cannot develop without long-continued precancerous changes in the tissue involved. To illustrate this point, he cited the case of an epithelioma developing after many years on the site of an extensive scar from an old burn. He, of course, did not correlate vitamin C deficiency to the connective-tissue breakdown. Bonney[7], in a study of precancerous changes, finds constant loss of connective tissue, usually hyaline changes in the collagen, and fraying of the edges of epithelial cells (Very suggestive of vitamin-C deficiency —W. J. McC.). He states: "In the area of primary carcinoma there has always occurred a complete disappearance of yellow tissue as a result of a pre-existent chronic inflammatory process, and it is in this de-elasticised area that the first epithelial down-growths occur". (Bonney had no knowledge of vitamin C.).

The recorded occurrence of multiple primary cancers (3.7 per cent of all cancerous cases according to U. S. statistics) indicates the presence of a systemic exciting factor. In 420 such cases reported by Warren and Gates (cited by Ewing) 111 had 3 or

more primary lesions, 67 had primary cancer in symmetrical organs, and 242 had primary cancer in 2 different organs. These findings would indicate that in certain persons there is a predisposition to cancer, which, in the opinion of the writer (W. J. McC.), could well be deficiency of vitamin C.

There are certain observations reported in the recent flare-up of research studies on lung cancer and tobacco smoking which seem to indicate a confirming correlation with the hypothesis of the etiologic relationship of vitamin C deficiency. In a report submitted by the American Cancer Society at the 1954 convention of the American Medical Association, the death rates of 187,000 men between the ages of 50 and 70 were checked for a period of 2½ years against their tobacco-smoking habits. In general it was found that the death rate from all causes was 60 to 102 per cent higher in cigarette smokers than in non-smokers. The death rate from lung cancer was 200 to 1500 per cent higher, depending upon the degree of addiction, and that of cancer in general was 150 per cent higher in cigarette smokers as a whole than in non-smokers.

These figures definitely indicate a systemic, as well as a local, cancerogenic effect from the tar and other toxic elements in the tobacco smoke; and according to the writer's hypothesis this might well be indirectly due to vitamin C deficiency. In this respect cigarette smoking has a three-fold impact on the human organism: (1) The respiratory mechanism is submitted to direct and repeated exposure to the specific cancerogenic tars of the burning tobacco. (It should be noted that these tars are not found in the tobacco plant, but are solely products of combustion and may be produced as readily in the burning of wood and paper, even cigarette paper, as shown recently, by Lafemine[8]). These tars act locally as an irritant to the respiratory tissues and thus stimulate cancerogenic reaction. Furthermore, this irritation, per se, causes local depletion of vitamin C needed in tissue repair. (2) The systemic absorption of the tars and other toxic elements, including nicotine and carbon monoxide, interacting chemically with the systemic storage of vitamin C (the latter being a powerful reducing and oxidizing agent) still further lowers the body level of this vitamin. (3) Smoking definitely distorts the dietary pattern of its habitues, in that they incline to the use of stimulating beverages

(tea, coffee, cola and alcohol) in preference to citrus, tomato and other fresh fruit and vegetable juices containing vitamin C. Thus the intake of this protective food element is reduced, while the body storage is depleted; and since the vitamin is water soluble and is constantly washing out of the system through the kidneys and perspiration, the body storage soon reaches a very low level.

During the past 15 years the writer has made close to 6,000 chemical tests of the body level of vitamin C, and in such tests on hundreds of steady smokers has yet to find a single case showing a normal level unless potent supplements of the vitamin are being taken. About ten years ago the writer determined by clinical and laboratory research that the smoking of one cigarette by the ordinary inhalation method resulted in the neutralization of 25 mg. of vitamin C in the body, or the equivalent of the vitamin C content of one average sized orange[9]. Thus the inability of the average smoker to attain a normal body level of this vitamin from dietary sources is quite apparent. The author's research in this respect has recently been confirmed by Bonquin and Masmanno[10] and by other investigators in Italy and Russia. It would thus seem possible that all cancerogenic agents, chemical and physical, act indirectly as such by reacting chemically with or increasing the body requirement of vitamin C.

A similar interaction has been found between certain chemical cancerogens and riboflavin, which also is known to have chemical reducing action. Kensler et al.[11] report marked inhibition of cancer induction by concurrent feeding of riboflavin with a well recognized chemical cancerogen. Later, Mueller and Miller[12] found this protective effect of riboflavin to be brought about by a reductive cleavage of the cancerogen, converting it into two non-cancerogenic compounds. It would thus appear that riboflavin is synergistic with vitamin C in cancer inhibition.

As a further check on this theory of indirect cancerogenesis the author made an in vitro experiment to determine the possibility of chemical interaction of vitamin C and the cancerogens. A small quantity of dibenzanthracine, a cancerogenic constituent of tobacco tar, was added to a solution of ascorbic acid of predetermined strength. A common solvent, dry alcohol, was used. A subsequent titration of the mixture showed a material drop in the ascorbic acid level. Presumably this reaction brought about a

proportionate reduction in the potency of the cancerogen. Similar experimentation, in vitro and in vivo, with other cancerogenic agents is anticipated. A comparable situation has prevailed regarding alcohol. For many years it was thought that alcohol was a specific cause of peripheral neuritis, a common affection in chronic alcoholism, but it is now known that deficiency of vitamin B_1 is the real culpable agent, the alcohol acting indirectly by increasing the body requirement of this vitamin.

Regarding cancer in infants and children: Lawrence and Donlan[13] state: "It seems clear that several types of embryonic tissue have a high degree of sensitivity to cancerogenic agents. The acute leukemias are an example of disease that may have such an origin. Leukemia seems to be increasing in incidence in recent years, especially in young children under 5 years, suggestively due to carcinogenic stimulation in prenatal life". (This suggests a possible correlation with the increase in smoking by women and the indirect production of vitamin C deficiency thereby in fetal life and early infancy by the mechanism previously described. —W. J. McC.)

All forms of physical and chemical irritation predisposing to malignancy, including trauma, thermal and electric burns, ultraviolet ray, x-ray, radium, atomic fission, chronic infections and inflammatory lesions, or exposure to toxic cancerogenic agents, are known to increase the body requirements for vitamin C, the lack of which increases vulnerability of body tissues to all such agents. Accordingly, vitamin C therapy is effective in minimizing tissue damage in all such conditions, thus serving to reduce potential malignancy.

Bodansky et al.[14] studied the vitamin C level of the blood plasma and the white blood cells in healthy subjects as compared to that of cancer cases. They found the levels in the latter to be significantly lower. Russell et al.[15] report that recurrent periods of scurvy, interspersed with periods of lettuce supplementation to prevent death, resulted in a significant shortening of the time of appearance of induced cancer in guinea pigs.

Schneider[16] cites Eickhorn as finding the vitamin C deficiency of cancer cases very pronounced, averaging 4,550 mg. by the saturation method, while his non-cancerous controls averaged only 1,350 mg. On the basis of these findings, he (Schneider) applied

intensive vitamin C therapy, 1,000 to 2,000 mg. daily, supplemented by vitamin A, in some hundred early and advanced cancer cases. He reports marked general improvement as shown in reduction in size of tumors, increase in body weight, lowered blood sedimentation rate, delayed cachexia, reduction in hemorrhage and ulceration. He obtained no complete cures. He considers the results as favorably comparable to sex hormone therapy in genital carcinomata, with the great advantage that it is at least harmless.

Regarding the concurrence of cancer and tuberculosis: Lebert, in 1852, stated that he had many times observed the coincidence of tubercle and cancer. This is so well recognized at the present time that the Index Medicus has a special sub-heading for "Cancer and Tuberculosis" under the index listing of "Cancer". The common factor in these two diseases would seem to be vitamin C deficiency, since both are known to be associated with pronounced C-avitaminosis.

Another suggestively significant observation reported by medical missionaries and in geographic research studies is the finding of large communities of primitive tribes in Africa, South America, Indonesia and certain islands of the Pacific ocean, to be almost completely immune to cancer. The food supply of all such people is mainly from natural sources, of which fresh fruits and vegetables, rich in vitamin C, form a prominent part.

It is not expected that the development of the writer's hypothesis, as herein advanced, will lead to a cure for cancer in its advanced or metastatic stages; but the prospects for prophylaxis and enhancement of surgical and radiation therapy by concurrent vitamin C therapy seem very encouraging. After all "an ounce of prevention is worth a pound of cure".

SUMMARY

After reviewing the history of cancer and the various theories of its cause, the writer advances the hypothesis of vitamin C deficiency, bringing about rupture of the sub-epithelial connective-tissue basement membrane, as the critical preconditioning factor in pathogenesis. A number of 19th century writers are cited as relating the cancerous invasion by epithelial cells to weakening and consequent failure of restraint by the supporting connective tissues. The author correlates these earlier concepts with our knowledge

of the function of vitamin C and observations of earlier writers on scurvy, and thus evolves this new etiologic approach. A number of research findings are cited which give direct or indirect support to the author's concept.

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COMPLICATIONS FOLLOWING VACCINATION WITH BCG. (Nederlandsch Tijdschrift v. Geneeskunde, Amsterdam, 97:2780, Oct. 24, 1953). For some time it was widely assumed that vaccination with BCG involved practically no danger. Follow-up studies on newborn infants given BCG by mouth, however, disclosed a relatively high incidence of complications. The present report reviews investigations carried out on 3,636 adolescents one year after vaccination with BCG. In 0.03% a scar of a perforated suppurative lymphadenitis was observed. Enlargement of the regional lymph nodes caused complaints in 0.8%, and in 6.7% the lymph nodes were enlarged without giving rise to complaints. Conjunctivitis possibly caused by BCG was observed in 0.24%. Erythema nodosum occurred in 0.1% and 0.4% experienced general malaise of several days duration. —*J.A.M.A.*

AMMONIACAL NAPKIN DERMATITIS IN INFANTS*

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Napkin dermatitis or "diaper rash" has plagued infants and mothers since the beginning of recorded time. Its incidence and severity has increased progressively with the development of clothing and of our aesthetic senses. At our present high level of progress in body covering and moisture and vapor-proof protection, napkin dermatitis is at a high level of incidence.

Two entities comprise the usual type of diaper area eruption. One is an intertrigenous dermatitis, caused by moisture and irritation on opposing areas of skin, and is usually found in tissue folds. It is most common in infants who have been permitted to remain in soiled or wet diapers for extended periods of time.

The other is an ammoniacal dermatitis, caused by contact with the skin of ammonia formed by the action of bacteria on the urea of the urine.[1-3] These bacteria, inhabitants of the intestinal tract, contaminate the diaper area constantly. They grow best in a slightly alkaline pH. The formation of ammonia, therefore, occurs most favorably in an alkaline urine, with a high nitrogen content and under conditions where urea splitting bacteria are flourishing in the intestinal tract.

Napkin dermatitis is most marked on the convex areas of the skin. When moisture and ammonia are kept in close contact with the skin, as when enclosed by a plastic or rubber diaper cover, the dermatitis may be severe. The double or triple diapered infant, whose diapers are maintained in close contact with the body by moisture proof covering, and who lies through the night while the warmth of his body promotes the growth of bacteria and the chemical reactions freeing ammonia, may awaken in the morning with his diaper area giving every appearance of a severe chemical burn or scald, which indeed it is.

In both types, the earliest lesion is an erythema. In severe ammoniacal forms, the earliest lesion may also include a fair degree of vesiculation. If the irritating process continues, there is papulation, which becomes confluent, and then a scaling dermatitis, having the appearance of an eczema, usually ensues.[4] In many

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cases there is some lichenification and xerosis of the superficial skin layers.

A special condition arising in circumcised male infants frequently occurs in conjunction with ammoniacal dermatitis.[5] The uretheral meatus and surrounding skin of the glans becomes red, swollen and encrusted. When this crust is removed, a raw bleeding area remains. Urination becomes painful and temporary retention of urine may be encouraged. In severe cases, cicatrization and contracture of the urinary meatus may arise, causing permanent narrowing of the stream, difficulty in urination and, occasionally, necessitating surgery to remedy the situation.

Therapy should be aimed at: 1. Relief of inflammation. 2. Drying up the diaper area. 3. Elimination of ammonia.

1. Usual therapy of acute inflammatory processes in the skin is the application of wet dressings of some isotonic or approximately isotonic electrolyte solution. In this type of dermatitis, however, it is more desirable to use a non-aqueous means of treatment for the acute inflammation, since one of the basic causes of the irritating and inflammatory process is an excess of moisture in contact with the skin for long periods, with a consequent macerating effect. We have found most effective in the early inflammatory phase of this condition, a smooth water-miscible cream.* There is a remarkable reduction of the inflammatory phase within 24 hours after initiation of therapy. The cream is applied liberally to the affected areas just before the new diaper is placed in position, and renewed each time a diaper change is made.

2. It is next to impossible to dry up the diaper area of an infant, but strenuous efforts must be made to keep the area as dry as possible. Diapers should be changed frequently, as soon as they are wet. After the wet diaper is removed, the area should be washed free of urine and allowed to dry in the air for 10 to 15 minutes. The heat from an electric light or infra-red bulb, kept of course at a safe distance, may be helpful here. A light coating of powder also helps absorb any residual moisture on the skin.

Such frequent changing is difficult and impractical during the night, and during this period the skin should be protected by a

*Panthoderm Cream. U. S. Vitamin Corporation, New York.

coating of some thick water resistant material, such as Lassar's paste, one of the protective silicones or similar materials.

3. There are a number of approaches to the problem of elimination of ammonia, none of them, in itself, of a high degree of effectiveness. The simplest step is temporary elimination of the use of the waterproof diaper covers. No matter how porous these are advertised to be, if they do an effective job of retaining the moisture in the wet diapers, they also will retain ammonia in high concentrations, in contact with the skin. Secondly, as a protective material, to keep the ammonia from attacking the skin, a thick ointment is of value.

Another line of attack is to try to minimize the growth and activity of the ammonia forming bacteria. This has been done with the use of various chemical inhibitors.[4, 5] Bichloride of mercury has been used in 1:4000 solution (one 0.5 gm. tablet to 2 quarts of water).[1] The washed diapers are impregnated with this solution, wrung out and allowed to dry. Objections to this method are that it necessitates keeping a poisonous substance in the household, but carelessness with poisonous materials of all kinds in the household is a hazard requiring constant vigilance. There has been no evidence of adverse effects by absorption of any of the material through lesions in the diaper area.

A saturated solution of boric acid has been used in a similar manner and is probably less effective. There seems to be little danger of absorbing enough boric acid to do any harm. The danger of boric acid poisoning is only present when the material is used as a dusting powder over relatively large areas of raw surface.

Various other chemical compounds have been used for this purpose, and are marketed under various trade names, e.g., Roccal[6], Diaperene[7]. These are non-volatile materials and have a low toxicity. Probably all of the impregnating materials have only a limited effectiveness in cutting down ammonia formation.

The metabolic approach is an interesting one. There are two lines of thought here. There have been claims for success made by merely acidifying the urine through the feeding of acid salts, such as monosodium phosphate. Others claim that primarily it is necessary to cut down the excretion of urea in the urine by maintaining a proper nitrogen balance. These authors claim success

by giving adequate carbohydrate and lower protein in the diet. Methionine 3 grains per day or thiamine 60 mgms. per day has been reported as effective in freeing the urine of excess ammonia formation, probably working through regulation of protein metabolism.[10]

One line of attack that has not been reported, and is now under study here, is the suppression of the intestinal flora responsible for ammonia formation by antibiotics and other means.

A proper regime for control of napkin dermatitis includes all the factors discussed above. Depending on the severity of the dermatitis, a few or all lines of therapy may have to be employed, but it should be done in an orderly manner, bearing constantly in mind the physiology and pathogenesis of the condition.

SUMMARY

1. Napkin dermatitis is caused by excessive moisture causing skin maceration, and ammonia causing direct chemical inflammatory reaction.

2. Therapy should be aimed at drying up the area and removing the ammonia.

3. Methods of achieving these results are discussed.

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PEDIATRICS AT THE TURN OF THE CENTURY

From time to time the Archives, which was the first Children's Journal in the English language, will reprint contributions by the pioneers of the specialty over fifty years ago. It is believed that our readers will be interested in reviewing such early pediatric thought.

PNEUMONIA IN INFANCY TREATED WITH ANTIPNEUMOCOCCIC SERUM.*

REPORT OF EIGHT CASES.

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During the last dozen years many attempts have been made to produce a serum of therapeutic value in the treatment of pneumonia in man. The Klemperers were the first to produce immunity experimentally. They used filtered cultures and succeeded in obtaining a serum which protected other animals against fatal pneumococcus infection. They were able to demonstrate a protective body in the blood which they termed antipneumotoxin. Its therapeutic value was, however, very feeble. Its action was largely, though not entirely, antitoxic. Many others have since worked on the same lines with more or less unsatisfactory results. Other investigators have used sera obtained from men ill with, or convalescing from, pneumonia. Their results have been equally unsatisfactory.

Later investigators, among the first of whom were Washbourne, De Renzi and Pane, have, by the use of living cultures, produced sera which protected against virulent pneumococci and possessed a certain therapeutic value. These sera exert a direct destructive action on the bacteria but probably have little or no effect on the separable toxines of the pneumococcus, that is, they are antiinefectious rather than antitoxic in their action. Such sera

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are therefore usually known as antipneumococcus sera. The results obtained in the treatment of pneumonia in man with these sera have been on the whole discouraging, although some few observers have reported very favorable figures. Goldsborough, about a year ago, collected the cases treated with the various sera and published a summary in the Journal of the American Medical Association. The cause of the failure of the antipneumococcus sera to give more satisfactory therapeutic results is presumably the same as in the case of the other antibacterial sera, and that is, that while they are rich in the immunizing body, they are probably lacking in the end-body or complement. If this complement can be provided they will probably become more effective. Investigation along this line seems, therefore, most likely to yield results of value in the serum treatment of pneumonia.

Through the courtesy of the H. K. Mulford Co., who furnished me with the serum, I have been able to test the antipneumococcic serum in 8 cases of pneumonia in infants. All were patients at The Infants' Hospital, Boston. For lack of a better basis of classification, I have arranged them according to the dosage and total amount of serum used. The serum was injected every four hours, while the temperature was taken in the rectum every two hours. No antipyretic treatment was used except in one case which received a few baths. The other treatment was limited to regulation of the diet and stimulation when necessary. A careful physical examination was made in every case before the serum was begun, daily during its use, and for some days after it was omitted. The blood was examined before and after its use in only 3 cases.

CASE REPORTS

Case 1. Mary M., aged nine months, had had a cold for two weeks. She suddenly became much more sick and developed a high temperature on January 7. She was admitted to The Infants' Hospital January 9.

She was fairly developed and nourished. There was slight cyanosis. The alae nasi moved with respiration. The heart was normal. There was slight dullness over the right lower lobe as far forward as the midaxillary line. At the root of the lobe, extending outward and downward about 4 cm., the respiration

and voice sounds were bronchial. Over the rest of the dull area the respiration was diminished and bronchovesicular in character. The voice sounds were slightly increased and numerous medium moist râles were heard. The rest of the examination was negative, except for slight evidences of rickets.

White blood corpuscles, 21,875. Urine: pale, turbid, acid, no albumin.

Five cc. of antipneumococcic serum were given every four hours.

January 10. There were flatness with bronchial respiration, bronchial voice sounds and high-pitched medium moist râles over the right lower lobe as far forward as the anterior axillary line. There were numerous moist râles over the rest of the lobe in front. There were also a few medium moist râles in the left back. The color was no better.

January 11. There was flatness with bronchial respiration over the same area as before but the respiration was diminished in intensity. There were a few high-pitched moist râles in the right lower back but none elsewhere.

The antipneumococcic serum was then omitted because the supply had failed. A total of 50 cc. was given.

January 12. White corpuscles, 18,125.

January 13. There were flatness with bronchial respiration, increased voice sounds and an occasional high-pitched moist râle over the right lower lobe.

January 14. Paracentesis was performed for an acute purulent inflammation of the right middle ear.

January 15. The signs of solidification were less marked. The temperature fell to normal by crisis on that day and remained there.

January 17. The lungs were clear.

This case came under observation so early and showed such definite signs that it seemed most suitable to test the value of the serum. The marked variations in the temperature are not unusual in the pneumonias of infancy. They were just as marked after the serum treatment was discontinued as before. The temperature both rose and fell immediately after the injections. The crisis occurred on the ninth day, rather later than is usual in infantile pneumonias. The solidification of the lungs increased after the serum treatment was begun. The rate of the pulse and

respiration was unaffected. The conclusion seems justified, therefore, that the serum had no effect either on the course of the disease or its symptoms.

Case 2. Harry R., aged seventeen months, had had a slight diarrhea, and had passed but little urine during the three weeks since a vaccination. The history was, however, very indefinite. The physician who sent the baby to the hospital thought that the pneumonia began January 2. He was admitted to The Infants' Hospital January 9.

He was a large, fat baby. The fontanel was level. The alae nasi moved with respiration. The heart was normal. There was marked dullness over the right upper lobe except in the lower part in front where there was tympany. There was bronchial respiration in the right front above the second rib inside the nipple line and above the fourth rib outside the nipple line. The voice sounds were bronchial over the same area. The respiration over the rest of the right upper lobe was bronchovesicular. The rest of the right lung and left lung were normal. The physical examination was otherwise negative, except for slight evidences of rickets. The general condition was good.

White corpuscles, 26,000.

Urine: high, acid, loaded with urates, albumin one-half per cent, or more. Sediment: urates, small round cells, a little normal blood, hyaline, fine granular and epithelial casts.

Five cc. of antipneumococcic serum, every four hours, was begun.

January 10. The heart sounds were strong. The second sound at the pulmonic orifice was the louder. The color was not as good. The lips were dry and bleeding. The lungs showed, in addition, a very few râles in the right upper lobe. The urine was unchanged.

January 11. Flatness with bronchial respiration and voice sounds had developed over the whole right upper lobe. No râles were heard. The rest of the chest was normal.

The antipneumococcic serum was omitted after 50 cc. had been given because of the failure of the supply.

January 12. White corpuscles, 47,000.

January 13. The lungs were unchanged. Paracentesis was done on both ears because of acute inflammation.

The temperature ranged normal after the 12th but never touched

normal. The signs of solidification began to diminish on January 17. The urine continued to show the same evidences of acute nephritis but was passed in fair amounts. The amount of urine fell off very decidedly on the 18th and very little was passed on the 19th. The urine on that day was thick and turbid and contained many small round cells, a very little normal blood, many hyaline, fine granular, brown granular and epithelial casts, and an occasional waxy cast. Marked symptoms of uremia developed during the 19th and death occurred in convulsions on the 20th.

The serum apparently had no effect whatever. The temperature was not influenced in any way. There was no reduction in the rate of the pulse or respiration. The physical signs increased while it was being used. The course of the disease was certainly not shortened. Inflammation developed in both middle ears. Whether this inflammation was due to the pneumococcus or not is unknown as the pus was not examined. Presumably it was. Death was caused by the nephritis which was active at entrance before the serum was used. There is no reason to suppose that the serum aggravated the process in the kidneys.

Case 3. David S., aged eight months, was admitted to The Infants' Hospital April 8, on the fourth day of an acute illness.

He was well developed and fairly nourished. The color was good. The alæ nasi moved with respiration, which was grunting. There was slight retraction of the lower chest with inspiration. Resonance was impaired over the whole of both chests. There was bronchial respiration over the right lower lobe as far forward as the posterior axillary line and downward to the eighth rib. The voice sounds were increased in this area, and an occasional high-pitched râle was heard. The rest of the lungs was clear. The examination was otherwise negative, except for slight evidences of rickets and slight enlargement of the spleen.

White count, 11,875.

The urine was high in color, highly acid and contained a trace of albumin. The sediment showed uric acid and an occasional fine granular and epithelial cast.

Five cc. of antipneumococcic serum were given every four hours.

April 10. There was flatness in the area of bronchial respiration and crepitant and medium moist râles were heard over the rest of the right lower lobe.

April 11. The signs were essentially the same although the râles were more numerous.

The antipneumococcic serum was omitted because of the fall in temperature. Ninety cc. had been given.

The temperature rose again, however, reaching 103° F. on the 12th. On the 13th it fell, that is the 9th day, by crisis and remained there. The lungs began to clear on the 12th and were practically normal on the 14th.

April 13. White count, 16,016.

This case also seemed a favorable one to study as the physical signs were well-marked and the serum was begun on the fourth day. It had no apparent effect, however. The temperature both rose and fell immediately after the injections. In spite of repeated injections it remained elevated until the seventh day when there was a pseudo-crisis. The serum was then omitted. The real crisis appeared on the ninth day. The physical signs increased, if anything, while the serum was being used. The rate of the pulse and respiration was unaffected.

Case 4. Mary W., aged sixteen months, was admitted to The Infants' Hospital May 11 without any history.

She was fairly developed and nourished. The alæ nasi moved with respiration, which was grunting. There was flatness in the right front below the third rib extending backward to the post-axillary line. The respiration and voice sounds were bronchial in this area, and an occasional high-pitched moist râle was heard. The rest of the right lung was normal. There was slight dullness with bronchovesicular respiration over the left lower lobe, more marked at the angle of the scapula and in the axilla. The voice sounds were somewhat increased and an occasional moist râle was heard. The examination was otherwise negative, except for slight evidences of rickets.

Five cc. of antipneumococcic serum were given every four hours.

May 14. There was no material change in the physical signs, although the evidences of solidification were rather more marked on the left. There were râles throughout both lungs. The general condition was not as good.

The antipneumococcic serum was omitted after 90 cc. had been given, as it seemed to be doing no good.

The temperature continued to range irregularly elevated, and an empyema developed on the right side.

This case was undoubtedly one of bronchopneumonia and perhaps, therefore, hardly a fair one on which to test the serum, as bronchopneumonia is often caused by other organisms than the pneumococcus. The temperature showed considerable daily variations, which continued after the serum was omitted. The temperature both rose and fell immediately after its use. It had no effect on the rate of the pulse and respiration. The physical signs increased slightly while it was being used. An empyema developed later.

Case 5. George G., aged eighteen months, had been a little out of sorts for two weeks but had shown no definite symptoms. He was taken suddenly sick April 11 and was admitted to The Infants' Hospital April 14.

He was well developed and nourished, but pale. The alæ nasi moved with respiration. There was dullness in the right back above the middle of the scapula with slightly changed respiration and prolonged expiration. The voice sounds were not changed and no râles were heard. The spleen was considerably enlarged. The examination was otherwise negative, except for moderate signs of rickets.

White corpuscles, 27,000.

Urine: high, acid, 1022, trace of albumin. Sediment: occasional small round cells, no casts.

April 17. There was slight dullness with bronchial respiration over the right upper lobe, back and front. The voice sounds were slightly increased but no râles were heard.

The antipneumococcic serum was first given at this time, that is, on the sixth day of the disease. Five cc. were ordered every four hours.

April 18 The signs were those of complete solidificatton of the right upper lobe.

April 20. The temperature fell nearly to normal in the morning, but rose again in the afternoon.

April 21. The right upper lobe showed no signs of resolution, but the bases of both lungs were full of fine, moist râles. There was also edema of the feet and hands but more of the face. The urine was high, acid and contained a slight trace of albumin. The sediment showed an occasional small round cell and hyaline cast.

The antipneumococcic serum was omitted because the tempera-

ture was normal. One hundred and fifteen cc. in all were given.

April 23. The edema of the feet and hands steadily increased, and death occurred as the result of cardiac failure.

The temperature both rose and fell immediately after the administration of the serum. It practically reached normal on the ninth day of the disease, three days after the serum was begun. This fall, coming as it did on the ninth day, can hardly, however, be attributed to the serum. It came unusually late for an uncomplicated pneumonia in an infant. The serum had no effect on the rate of the pulse and respiration. The process in the lung became more intense while it was being used. Death followed as the result of cardiac failure due, in all probability, to toxemia. The serum was certainly of no utility in this case.

Case 6. Jennie F., aged twenty-two months, was taken suddenly ill June 9 with fever, cough and dyspnea. A diagnosis of bronchitis was made June 10 by some physician. The diagnosis of pneumonia was made June 17 by another physician and she was admitted to The Infants' Hospital the same day.

She was well developed and nourished and of good color. The alæ nasi moved with respiration. There was dullness with bronchovesicular respiration, increased voice sounds and occassional râles over the left upper lobe. The examination was otherwise negative, except for slight evidences of rickets.

Treatment with the antipneumococcic serum was begun at once. Ten cc. were given every four hours.

June 18. In the morning the left upper lobe showed all the signs of complete solidification. The general condition was somewhat better. The crisis occurred that afternoon, and the temperature did not rise again.

The serum was omitted after the crisis, 70 cc. having been given.

Resolution began June 19 and the lungs were practically clear June 21.

The temperature both rose and fell immediately after the use of the serum. If we consider, as is probably true, that the pneumonia began on June 9 and that the diagnosis of bronchitis was wrong then treatment was not begun until the seventh day of the disease and the crisis occurred on the eighth day. In this case of course it could not be attributed to the serum. If we assume that the diagnosis of bronchitis was correct and that the pneumonia did

not begin until June 17, then the crisis occurred on the second day and might be attributed to the use of the serum. As, however, the signs of solidification were well marked at entrance, and there were no evidences of bronchitis elsewhere, the diagnosis of bronchitis was undoubtedly wrong. The crisis occurred on the eighth day, therefore, and was not due to the serum. The physical signs increased after the serum was begun. No effect on the rate of the pulse or respiration was noted.

Case 7. Frank T., aged twenty-four months, entered The Infants' Hospital April 28 with an indefinite history of a week's illness.

He was a well developed and fairly nourished negro. The alæ nasi moved with respiration, which was grunting. The right border of cardiac dullness was 3 cm. to the right of the median line. The heart sounds were louder to the left than to the right of the sternum. The left side moved less than the right. There was no bulging of the intercostal spaces. There was an area of flatness coinciding with the left lower lobe. There was slight dullness in Traube's space. There was loud bronchial respiration over the left lower lobe, except at the extreme base, where it was diminished. The voice sounds were increased; the fremitus was not determined. No râles were heard. The examination was otherwise negative except for slight signs of rickets.

Urine: high, acid, turbid, no albumin.

April 29. Treatment with antipneumococcic serum was begun, 10 cc. being given every four hours.

April 30. The serum was omitted after 80 cc. had been given because the supply was exhausted.

May 1. The heart was in normal position. There was dullness in Traube's space. There was flatness over the left lower lobe with bronchial respiration and voice sounds and an occasional high-pitched râle.

The temperature continued elevated. On May 3 the heart was somewhat displaced and there were the signs of a small amount of fluid in the left chest. Exploratory puncture was negative. The temperature continued elevated and the signs of fluid increased. On May 7 pus was obtained by puncture. The patient ultimately recovered.

In this case the temperature neither rose nor fell after the use

of the serum. The signs in the lungs did not change during its use. An empyema developed afterward. No effect on the rate of the pulse or respiration was noted.

Case 8. Kaleel O., aged fourteen months, was admitted to The Infants' Hospital June 19 without history.

He was well developed and nourished and of good color. The alæ nasi moved with respiration which was grunting. There was dullness over the whole right lower lobe with slightly modified vesicular respiration. The voice sounds were slightly, and the fremitus considerably, increased. There were no râles. The examination was otherwise negative, except for slight evidences of rickets.

Urine: high, acid, no albumin.

Although the temperature was low the antipneumococcic serum was begun on the 20th, 10 cc. being given every four hours.

June 22. There was dullness over the whole right back with bronchovesicular respiration, increased voice sounds and fremitus. There was flatness over the right front with bronchovesicular respiration at the upper part. Elsewhere it was normal.

June 23. The serum was omitted after 180 cc. had been given, because it was absorbed poorly. Both thighs were swollen, indurated and tender as the result of the injections.

The signs of solidification were somewhat more marked. The temperature fell to normal by crisis that night and did not rise again.

The signs of solidification quickly cleared up. The induration of the thighs was gone by June 27.

This case shows the marked variations in temperature so often seen in the pneumonias of infancy. They were evidently not influenced by the injections of serum as the temperature both rose and fell after them. On account of the absence of history it was impossible to tell whether or not the serum shortened the course of the disease. The physical signs increased, however, while it was being used. This is the only case in which the serum was not well absorbed and caused any induration. This disappeared rapidly and did no harm. No effect on the rate of the pulse or respiration was noted.

In no case did the serum have any perceptible effect on the temperature. In 6 it both rose and fell immediately after the in-

jection, while in 2 (Cases 2 and 7) the variations immediately after the injections were insignificant. In no case in which the time of the onset could be determined was the course of the disease shortened (Cases 1, 3, 5, 6 and 7). In fact, the crisis occurred later in these cases than is usual in the pneumonias of infants, coming on the eighth day in 1 (Case 6) and on the ninth day in 3 (Cases 1, 3 and 5). An empyema developed in the other (Case 7) without there having been any fall in the temperature.

No effect on the rate of the pulse or respiration was noted in any case.

Several observers have noted that in adults the subjective symptoms were relieved for a time after each injection of serum. In infants it is, of course, extremely difficult to estimate variations in the degree of the subjective symptoms. Nothing was noticed in these cases, however, to justify the assumption that they were in any way modified by the serum.

The physical signs increased in 6 cases while the serum was being used (Cases 1, 2, 3, 4, 5 and 8). In the others (Cases 6 and 7), in which the serum was not used until late in the disease, there was no change.

Two (Cases 1 and 2) cases developed purulent inflammation of the middle ears, and 2 (Cases 4 and 7) developed empyema. Two (Cases 2 and 5) died; 1 (Case 2) of nephritis, and 1 (Case 5) of cardiac failure. In neither case was there anything to show that death was due to, or hastened by, the use of the serum. The serum was well absorbed in all the cases but 1 (Case 8), in which it caused swelling, tenderness and induration about the seat of injection. These disappeared in a week. There were no rashes, joint symptoms, or late rises in temperature as the result of the injections.

The blood examinations were too few (Cases 1, 2 and 3) to be of any value, and the results were, moreover, not uniform. In an adult case on my service at the Boston City Hospital, in which examinations of the blood were made more often, there was usually a slight diminution in the number of leukocytes after the injection of the serum. Taken as a whole, there was a decided drop in the number of leukocytes after the serum was begun which persisted as long as it was continued. There was a slight rise again after it was omitted.

CONCLUSIONS

In these cases the antipneumococcic serum had no effect on the duration of the disease, the course of the temperature, the rate of the pulse and respiration or the progress of the local condition. Complications occurred at least as frequently as is usual. Death occurred in an unusually large percentage. The serum, while it apparently did no good, certainly did no harm.

FAMILIAL INCIDENCE OF CONGENITAL MALFORMATION OF HEART. (British Heart Journal, London, 15:273, July 1953). The familial incidence of congenital heart disease was recorded for 425 families which contained 431 probands born to Birmingham mothers between 1940 and 1949. The diagnosis of congenital malformation of the heart was established in the proband by postmortem examination, at operation, or clinically by a consultant physician. There were six affected by congenital heart disease (18 per 1,000) among 342 siblings born after the proband. This is approximately six times the incidence (3.2 per 1,000) in the general population of births. The incidence of malformations other than congenital heart disease was not raised in siblings of probands. The nature of the cardiac defects was fairly reliably diagnosed in five families with two affected members; in three of the five families the lesions were identical in both persons affected. This evidence suggests that the risk of recurrence of the same cardiac malformation may be greater than the risk of a different one. Five confirmed and 13 unconfirmed cases of congenital malformation of the heart were identified among 4,143 first cousins of probands. Of 834 parents, 14 were said to have congenital heart lesions. Further clinical examination indicated that eight of them were normal, four had rheumatic heart disease, and only two had congenital heart lesions. There were two marriages of first cousins among 424 marriages of parents of probands; in both cases, the proband had dextrocardia and transposition of the viscera. There were seven patients with dextrocardia among the probands, and the high incidence of consanguinity of parents in these cases provides support for Cockayne's suggestion that this condition may be inherited as a recessive.—*Journal A.M.A.*

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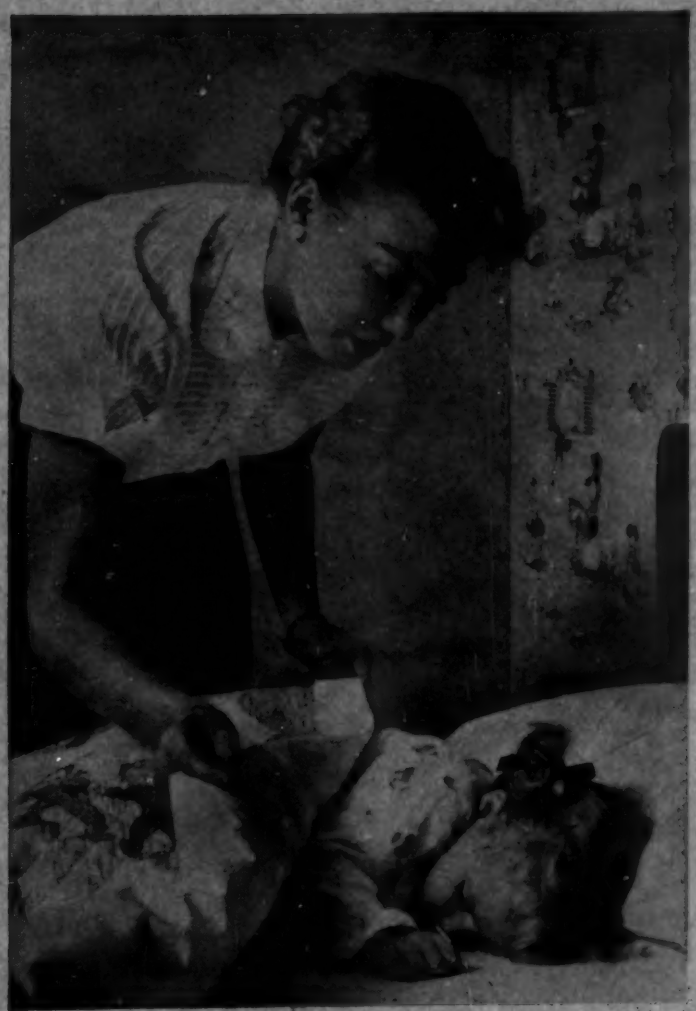

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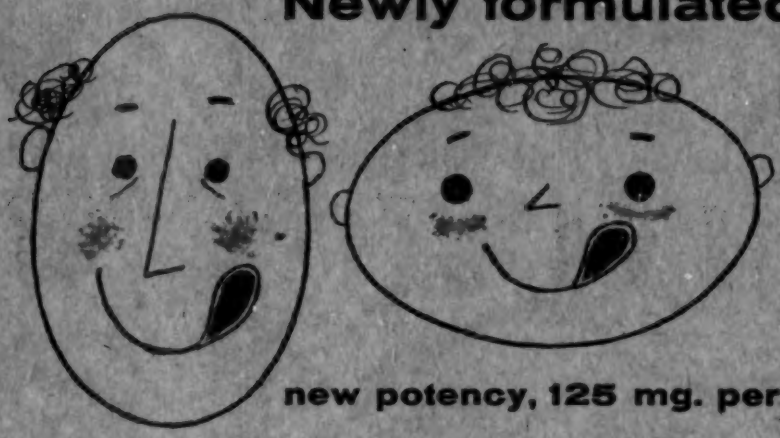

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